Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens

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Objective: To describe the various complications that have been reported with use of midazolam for sedation in the intensive care unit (ICU).

Data Sources: Publications in scientific literature.

Data Extraction: Computer search of the literature.

Synthesis: Sedation is required in the ICU in order for patients to tolerate noxious stimuli, particularly mechanical ventilation. Under- and oversedation can lead to complications. To sedate patients in the ICU, midazolam is commonly administered via titrated, continuous infusions. Cardiorespiratory effects tend to be minimal; however, hypotension can occur in hypovolemic patients. Prolonged sedation after cessation of the midazolam infusion may be caused by altered kinetics of the drug in critically ill patients or by accumulation of active metabolites. In addition, paradoxical and psychotic reactions have been rarely reported. Tolerance and tachyphylaxis may occur, particularly with longer-term infusions (≥3 days). Benzodiazepine withdrawal syndrome has also been associated with high dose/long-term midazolam infusions. Compared with propofol infusions, midazolam infusions have been associated with a decreased occurrence of hypotension but a more variable time course for recovery of function after the cessation of the infusion. Lorazepam is a more cost-effective choice for long-term (>24 hrs) sedation.

Conclusion: Continuous infusion midazolam provides effective sedation in the ICU with few complications overall, especially when the dose is titrated. (Crit Care Med 1998; 26:947–956)

KEY WORDS: sedation; intensive care; midazolam; intravenous; complications; propofol; lorazepam; critical care; mechanical ventilation; withdrawal; tolerance; infusion

Critically ill patients, particularly those requiring intubation and mechanical ventilation, usually need pharmacologic sedation to tolerate the multiple noxious stimuli associated with intensive care. A variety of drugs are available for the induction and maintenance of sedation of critically ill patients. Due to its safety and efficacy, midazolam is a popular drug used for sedating mechanically ventilated patients in the intensive care unit (ICU). Midazolam is commonly administered by continuous infusion to allow titration of the drug according to the desired level of sedation. However, complications with the use of this drug have been reported. This paper will review the role and potential complications of midazolam use in the ICU and compare studies of midazolam infusion regimens with those of other sedative drugs, such as lorazepam and propofol.

ROLE OF SEDATION IN THE INTENSIVE CARE UNIT

Sedation is often beneficial for ICU patients and usually required for tolerance of mechanical ventilation and noxious stimuli (1). Patient comfort can help stabilize hemodynamics and modulate stress responses, thereby contributing to the healing process (2). Goals of sedation include anxiolysis and reduction in motor activity, which would optimize mechanical ventilation and allow other procedures to be tolerated (3). Amnesia, respiratory depression (to facilitate mechanical ventilation if the patient's movements or breathing efforts cause high airway pressures), and an antitussive effect may also be desirable in some situations (4). Sedation is also advocated because it facilitates sleep, thereby avoiding prolonged ventilatory support due to sleep deprivation (5). Sedative-analgesic regimens are combination therapies which include pain relief as a goal.

The desired level of sedation for the critically ill patient has undergone an important change. In 67% of ICUs in 1981, the goal of sedation was to completely detach patients from their environment (6). However, a survey published 6 yrs later (7) observed that the goal of sedation had changed; the majority of ICUs now seek to maintain a patient who is sleepy but easily awakened. Nonetheless, there is no single desirable depth of sedation or sedative regimen appropriate for all patients (4). Titration of the sedative dosages and adjustment of the sedative regimen should be done continuously, as dictated by repeated assessments of the patient's needs and current level of sedation. Furthermore, weaning from the ventilator should be anticipated and the sedative regimen should be adjusted accordingly. Ideally, weaning from the ventilator should be rapid and should avoid agitation.

Complications of Sedation

Sedative drugs in the critically ill may contribute to increased morbidity, and possibly mortality (2, 4, 8, 9).

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Frequently, in the critically ill population, a drug side effect, such as mild hypotension, becomes a complication because of the potential for adverse consequences. Many sedatives cause adverse effects that restrict their use in the critically ill patient. These effects include cardiorespiratory depression (e.g., barbiturates), decreased gastrointestinal motility (e.g., opioids), increased intracranial pressure (e.g., ketamine), and extrapyramidal symptoms (e.g., antipsychotics such as haloperidol) (10, 11). Etomidate, used for sedation of ICU patients, was associated with an increased mortality rate of multiple trauma patients due to adrenal cortical suppression (9).

Both under- and oversedation can add risk to the clinical course of critically ill patients (Table 1). The level of sedation is not always simple to assess. For instance, the presence of autonomic responses, such as hypertension and tachycardia in response to stimulation, does not necessarily indicate that sedation is inadequate (12). To overcome some problems of inadvertent oversedation, routine sedation scoring, such as the Ramsey score which was designed to measure drug-induced sedation (13), should be used in all patients. Limitations of scoring systems include reliance on motor responsiveness for assessment—the scale must be modified when muscle relaxants are administered (14). The validity of a scoring system is difficult to assess due to factors such as variable end points, overlapping categories, and failure to differentiate pain from other sources of agitation (15, 16). Empirical methods which rely on subjective criteria and past experience to establish the level and quality of sedation are less efficient in maintaining appropriate levels of sedation than those methods which rely on standardized scoring systems (Fig. 1) (17). Multiple scaling systems, such as the Vancouver sedative recovery and COMFORT scales, are being investigated (18–22). Current work on neurophysiologic monitoring, such as bispectral analysis, and other objective parameters may lead to improved methods of sedation level assessment and, hence, management of sedative regimens (14, 23, 24).

Table 1. The risks of under- and oversedation

Risks of Undersedation	Risks of Oversedation
Hypertension	Hypotension
Tachycardia	Bradycardia
Discomfort	Coma
Hypoxia and hypercapnia (from failure of ventilator to work in synchrony with the patient)	Respiratory depression Ileus Renal failure Venous stasis Immunosuppression

Adapted from Burns et al (4).

Sedative-hypnotics and opioids are commonly administered by continuous intravenous infusion (1). Advantages provided by continuous infusion include circumvention of both high-plasma drug concentrations, resulting from administration of the large bolus doses required of an intermittent technique, and also of the low-plasma drug concentrations that can occur before the administration of the next bolus. When appropriately titrated, continuous infusion of a sedative drug minimizes periods of both the over- and undersedation associated with intermittent bolus administration (25). The presence of organ or multiple organ system failure will make titration attempts more difficult.

Midazolam Continuous Infusions

Midazolam offers multiple advantages for sedation in the ICU, including its compatibility with intravenous solutions, stability in aqueous solutions, absence of pain at the injection site, and reduced incidence of thrombophlebitis (26). Due to its high lipophilicity at physiologic pH, midazolam has a rapid onset of sedative effects. Midazolam has a high therapeutic index. Although there are cardiovascular changes with midazolam administration, these are usually mild with sedative doses (26, 27). Midazolam does not suppress the adrenal glands (Fig. 2) (27). Compared with the administration of benzodiazepines with longer elimination half-lives, the usually short elimination half-life of midazolam accounts for less drug accumulation and rapid recovery after prolonged administration (28). Additionally, in patients with normal renal function, the elimination half-life of the active metabolite of midazolam, 1-hydroxymidazolam (α-hydroxymidazolam), is only 1 hr (1). Finally, a specific benzodiazepine antagonist, flumazenil, is available for reversal of midazolam's sedative effects.

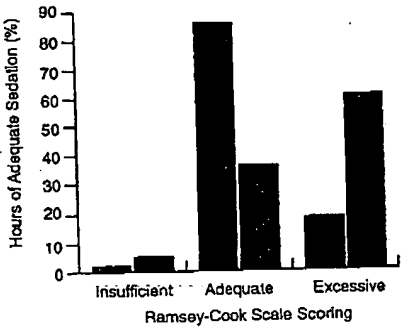

Figure 1. Quality of sedation achieved with either the controlled method (*solid bar*, dosing adjusted according to score on the Ramsey Sedation Scale and modified Glasgow Coma Scale) or the empirical method (*hatched bar*, dosing adjusted according to observation and past experience without scoring systems) of midazolam infusion. Adapted from Costa et al (17).

The administration of midazolam by continuous intravenous infusion for the induction and maintenance of sedation in an intubated ICU patient represents an extension of its currently approved use. The patient is protected from airway obstruction or respiratory depression by endotracheal intubation and mechanical ventilation. Continuous monitoring of the patient's vital signs and clinical status allows for close individualized titration of the sedation level.

Continuous infusion allows for greater controlled administration which minimizes high blood concentrations and avoids subtherapeutic levels (29, 30). In controlled settings, continuous infusion techniques of other drugs (i.e., fentanyl, alfentanil, ketamine, morphine, and propofol)

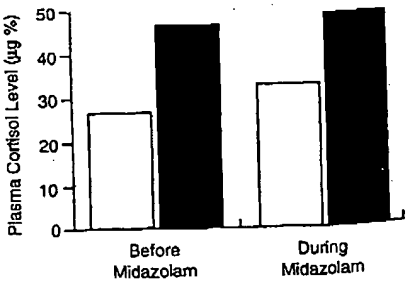

Figure 2. Cortisol (μg%) response to adrenocorticotropic hormone (ACTH) injection before and during midazolam infusion. *Open bar*, before ACTH injection; *solid bar*, after ACTH injection. Adapted from Geller et al (27).

have demonstrated lower doses when compared with intermittent bolus techniques, but such data are not available for midazolam for sedation in the ICU setting (31–34).

The safety profile of midazolam, when administered as a continuous intravenous infusion in critically ill patients requiring mechanical ventilatory support, is similar to that of short-term use of parenteral midazolam for conscious sedation and coinduction of anesthesia. Data from clinical trials (35–37) reported that continuous infusion of midazolam provides effective sedation with a low incidence of adverse effects.

COMPLICATIONS OF MIDAZOLAM INFUSIONS

Cardiovascular Complications

In the ICU, the most commonly observed adverse event reported in clinical trials of midazolam has been hypotension. The incidence of hypotension reported in patients treated with continuous intravenous infusion of midazolam ranges from 2.1% to 14.3%. Hypotensive episodes have been transient and mild in nature, with few patients having experienced >20% decrease in systolic blood pressure. Reports of hypotension requiring fluids or administration of a benzodiazepine antagonist were reported more frequently in patients during the loading dose of midazolam (38, 39). In patients with severe vasoconstriction, hypothermia, and possible hypovolemia, hypotension requiring intervention responded rapidly to fluid loading (39–41).

A number of studies have reported no differences in vasoactive drug requirements between patient groups treated with midazolam and comparison agents, such as propofol (10, 39, 42, 43). However, ICU patients treated with diazepam required increased use of vasoactive agents compared with those treated with midazolam (28). Westphal et al. (36) reported a decreased requirement for vasodilator infusions in patients receiving midazolam in doses of 2 mg/hr compared with those patients treated with midazolam in doses of 1 mg/hr.

Postcoronary revascularization patients exhibited a statistically significant increase in mean heart rate (from a baseline of 80 to 90 beats/min after 6 hrs) during a midazolam infusion. However, cardiac index and blood pressures were unchanged, and there was no evidence of myocardial ischemia (43).

Thus, midazolam, when given as a continuous intravenous infusion to critically ill patients, is usually associated with a stable hemodynamic profile (Fig. 3) (27, 44). However, caution should be exercised when initiating midazolam sedation with a loading dose in patients with preexisting hypotension, hypovolemia, vasoconstriction, and/or hypothermia.

Respiratory Complications

Induction doses of midazolam reduce the ventilatory response to CO_2, decrease minute ventilation, and can cause apnea (26). In a study comparing midazolam with propofol, the induction dose of midazolam was associated with a reduction of tidal volume of 200 mL for several mins in all patients and transitory apnea in three patients. Propofol induction produced transitory apnea in all 11 patients (45). However, in the patient who is undergoing mechanical ventilation, airway obstruction and respiratory depression are not issues. Because patients in the ICU are intensively monitored, few respiratory complications have been reported when midazolam is administered by continuous intravenous infusion. In patients with prolonged sedation, respiratory depression can delay weaning from the ventilator. A benzodiazepine antagonist, such as flumazenil, should be available to reverse the effects of midazolam, if needed. Although some controversy exists in the literature regarding the effectiveness of flumazenil for reversal of respiratory depressant effects of midazolam, recent work (46–49) confirmed the efficacy of flumazenil for this purpose.

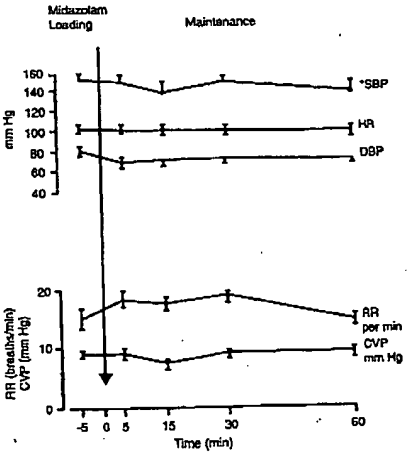

Figure 3. Hemodynamic and respiratory effects (mean ± SEM) of midazolam loading in 23 patients. The loading dose ranged from 0.05 to 0.15 mg/kg, administered over 10 to 20 mins. The maintenance infusion rate was 5.4 ± 2.4 mg/hr. *Significant difference in systolic blood pressure (*SBP*) during midazolam administration ($p < .03$); *HR*, heart rate; *DBP*, diastolic blood pressure; *RR*, respiratory rate; *CVP*, central venous pressure. Adapted from Geller et al (27).

Prolonged Sedation

Prolongation of sedation after discontinuation of a midazolam infusion can have multiple causes. A prolonged midazolam elimination half-life has been correlated with the severity of the patient's disease (50–52). Multiple organ system failure is associated with increased volumes of distribution and prolonged elimination half-lives in excess of 24 hrs (53). Prolonged elimination half-life was attributed to increased volume of distribution in a study (54) of critically ill patients, as clearance values did not differ from healthy volunteers.

The rate of metabolism for midazolam is dependent on hepatic metabolic capacity, the fraction of unbound drug, and hepatic blood flow. Thus, reduction in liver perfusion reduces the rate of midazolam metabolism (50). Cimetidine, which binds to the cytochrome P_{450} group of enzymes, increases steady-state plasma concentrations of midazolam, even after a single dose in healthy volunteers (51). One study (55) noted the inhibition of cytochrome P_{450} 3A4 activity (as measured by the rate of appearance of midazolam metabolite) in the presence of serum from critically ill patients. Concurrent administration of erythromycin has been cited as a possible cause of prolonged sedation of a pediatric ICU patient receiving midazolam (56). Midazolam has an active hydroxylated metabolite, which can contribute to a prolonged sedative effect (52). Bauer and colleagues (57) demonstrated that prolonged sedation can also occur due to accumulation of the conjugated metabolites of midazolam. Although the conjugated

metabolite, glucuronidated α-hydroxymidazolam, is one tenth as potent as the parent drug, accumulation of the metabolite in renal failure patients can lead to a significantly prolonged sedative effect (57).

Bodenham et al. (58) reported a patient in whom the consciousness level remained depressed 36 hrs after discontinuation of midazolam. Wakefulness in this patient was maintained by a flumazenil infusion of 8 days duration. Due to the limited duration of effect of flumazenil, an infusion may be required to maintain wakefulness (5). Ortiz et al. (59) reported an elderly patient with prolonged neurologic depression after 36 hrs of midazolam continuous infusion. The patient remained stable but without signs of awakening for 6 days; administration of 0.2 mg of flumazenil was followed by recovered consciousness, tachycardia, hypertension, and intolerance to tracheal intubation. The intensity and prolongation of neurologic depression associated with midazolam were considered unusual and were associated with the advanced age of the patient, concurrent renal insufficiency, and hypoalbuminemia. Two of eight patients who recovered from severe tetanus and who required midazolam infusions of 10 to 50 days duration had prolonged sedative effects (≤72 hrs) after cessation of the infusion (60).

Titration of the midazolam infusion rate to sedation level is predicted to help minimize prolonged sedation after cessation of the infusion (Fig. 4) (1). To manage excessive sedation in a patient who received midazolam continuous infusion, a 50% reduction of the infusion rate was recommended until the desired level of sedation was achieved (37). In one report, the midazolam infusion was adjusted as often as necessary to maintain a sedation level between 3 and 5 on a modified Ramsay sedation scale (13), which ranged from 0 to 6 (35). If a patient became oversedated (sedation level of 6), the midazolam infusion was stopped until the subject had attained a sedation level of 4, at which time the infusion was reinitiated at 50% of the initial rate.

In general, sedation levels are easily controlled with titration of midazolam infusion, and the incidence of prolonged sedative effects is thereby minimized. Additionally, one can administer the benzodiazepine antagonist flumazenil to increase patient wakefulness (61). Use of specific reversal agents may also help differentiate sedation from drug effect vs. underlying pathology such as encephalopathy (62). Flumazenil can be expected to cause arousal from midazolam-induced sedation for ~15 mins after an assessment dose (63). Adverse effects of flumazenil titrated to effect are rare, but resedation is possible, thereby necessitating a flumazenil infusion. Unmasking proconvulsant and dysrhythmic effects of other drugs has been reported after flumazenil administration (49, 64–67). The midazolam dose should be individualized with the infusion rate titrated according to clinical requirements, the patient's clinical status, the patient's age, and concomitant medications.

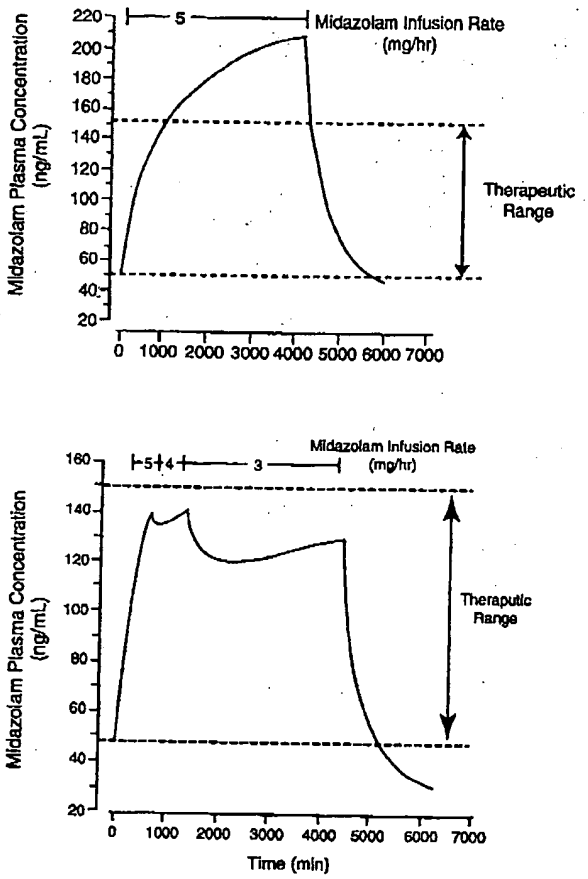

Figure 4. A comparison of untitrated vs. titrated midazolam infusion regimens. Predicted midazolam plasma concentrations resulting from an infusion of 5 mg/hr for 3 days (*top*). Predicted midazolam plasma concentrations after an initial intravenous bolus of 2 mg, then a continuous intravenous infusion of 5 mg/hr × 12 hrs, then 4 mg/hr × 12 hrs, and then 3 mg/hr, thereafter (based on Donner parameters) (*bottom*). Adapted from Barr and Donner (1).

Paradoxical and Psychotic Reactions

Agitation is an uncommon complication of midazolam infusion. Unlike withdrawal phenomena, which may occur after the discontinuation of a midazolam infusion, paradoxical reactions occur during the early stages of midazolam administration. Disorientation and impaired comprehension were common when a midazolam infusion was used in conjunction with morphine (68); however, it is unclear whether this response was due to inadequate sedation or the patients' underlying conditions. Thirteen percent of postvascular surgery patients receiving midazolam infusions experienced hallucinations during the infusion period; however, the authors noted that psychopathology is a common phenomenon in the ICU environment and could

not definitely determine the etiology of the hallucinations (35). Hughes et al. (69) reported a pediatric patient who became agitated with visual hallucinations 12 hrs after initiation of a midazolam infusion. Because paradoxical reactions are uncommon in the ICU setting, other causes of agitation, such as inadequate sedation, inadequate ventilation, and underlying conditions predisposing to psychosis, should be sought. If an increase in the midazolam infusion rate does not improve sedative conditions in an agitated patient who does not have a known cause for the agitation, then a paradoxical reaction should be considered and alternative drug therapy should be initiated. Haloperidol infusions have been used for refractory agitation in patients requiring mechanical ventilation (70).

Tolerance and Tachyphylaxis

If tolerance, the occurrence of diminished pharmacologic responsiveness to drug administration, appears over a short time frame, then it is termed acute tolerance or tachyphylaxis (71). The appearance of tolerance to midazolam and tolerance to midazolam induced by other benzodiazepines has been reported in humans (37) and in laboratory studies (72–74).

The development of tolerance to midazolam was demonstrated in a study of 50 consecutive ICU patients (75). Figure 5 depicts an unchanged sedation score but an increase in mean daily dose of midazolam. The tolerance phenomenon was also seen in a subgroup of 15 patients who received midazolam by continuous intravenous infusion for >7 days (Fig. 6). Withdrawal effects were not observed in these patients.

Failure to attain adequate sedation with appropriate doses of midazolam may be a result of tachyphylaxis. For example, in a pediatric ICU, when fentanyl (7 to 13 μg/kg/hr) and midazolam (≤0.4 mg/kg/hr) infusions failed to adequately sedate mechanically ventilated infants, pentobarbital infusions were necessary (76). Another study in adult cardiovascular surgery patients noted that tachyphylaxis was associated with intravenous drugs such as fentanyl and midazolam, but tachyphylaxis was not associated with isoflurane sedation (77). It may be necessary to switch sedation regimens to avoid accumulation of drug and metabolites if tachyphylaxis results in high infusion rate requirements.

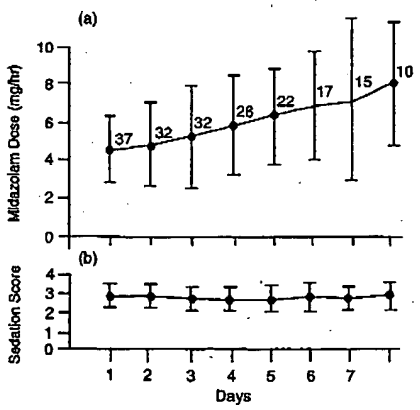

Figure 5. Mean daily dose of midazolam (*a*) and sedation score for all patients receiving a continuous infusion of midazolam (*b*). The number of patients considered at each time point is indicated. Adapted from Shelly et al (75).

Withdrawal

Withdrawal syndromes have been reported (78–80) when midazolam infusion is ceased. Signs and symptoms of benzodiazepine withdrawal may include seizures, tremor, confusion, hallucinations, anxiety, agitation, inability to communicate, insomnia, vomiting, tachycardia, and fever. It is sometimes difficult to assess whether these phenomena are due to withdrawal of benzodiazepines or to another drug or disease state. For instance, confusion in the postoperative ICU patient after cessation of a midazolam infusion may be more related to the ICU environment or other factors, rather than residual drug effect or withdrawal (35). However, temporal association of symptoms with benzodiazepine cessation and relief of symptoms with reinstatement of benzodiazepine treatment are evidence of withdrawal (80). Withdrawal symptoms may be more severe after cessation of shorter-acting rather than longer-acting benzodiazepines (81).

Withdrawal phenomena have been reported more commonly with higher-dose midazolam infusions of >3 to 5 days duration compared with brief infusion regimens (40, 78, 82). For instance, after 12 days of a midazolam infusion, extreme anxiety, hypertension, and tachycardia occurred in a 30-yr-old critically ill patient during a rapid tapering of the infusion for weaning purposes (40). After a 33-day

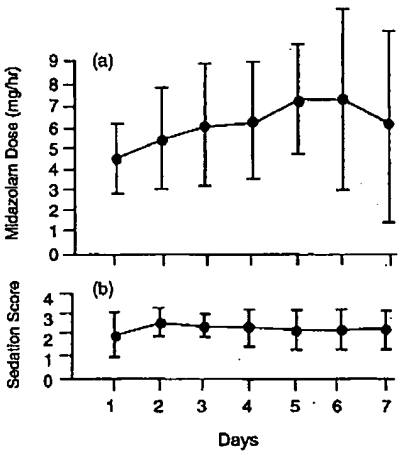

Figure 6. Mean daily dose of midazolam (*a*) and sedation score for 15 patients who received a continuous infusion of midazolam for ≥7 days (*b*). Adapted from Shelly et al (75).

midazolam infusion and a total dose of 13,440 mg of midazolam, a patient exhibited anxiety, tremor, insomnia, agitation, and paroxysmal activity on electrocardiogram, all of which resolved with reintroduction of midazolam infusion and a slower tapering of drug (78). Four of 53 pediatric patients exhibited hallucinations and other withdrawal phenomena after discontinuation of midazolam infusions (infusions ranged from 1 to 8 days) (69). Pediatric patients with severe withdrawal syndrome after discontinuation of a midazolam infusion may exhibit gastrointestinal symptoms due to aerophagia (83).

When large doses of midazolam have been administered over long periods of time, the clinician should use a tapering

regimen of intravenous midazolam over several days to minimize withdrawal symptoms. While midazolam concentrations decline relatively slowly after an infusion, reduction of the infusion rate by 50% decrements is preferred to abrupt discontinuation. This approach permits careful reappraisal of the patient's underlying condition to avoid a sudden return of agitation, requiring reloading of the sedative agent and a general setback to the patient's progress, and is more compatible with ICU conditions in which stimulation can change rapidly (37). Alternatively, a transition to long-acting benzodiazepines may be of benefit (81, 84), although seizures have been reported even after a transition from long-term midazolam infusion to oral diazepam (79). Patients should be monitored for signs and symptoms consistent with drug withdrawal when midazolam infusion is discontinued.

Interactions with Opioids

In general, opioid requirements will decrease if sedatives, such as midazolam infusions, are administered (16). Opioids and midazolam have been found to be at least additive and frequently synergistic with regard to sedative effect (85–88). In the ICU, average postoperative morphine requirements were higher (43 vs. 18 mg) in the low (0.5 μg/kg/min) vs. high (1.5 μg/kg/min) midazolam infusion groups (initial settings) (35). A similar difference in morphine requirements was noted in postcardiac surgery patients, depending on low vs. high dose midazolam (36). Pediatric burn patients require lower morphine doses when simultaneous midazolam infusions are used (89).

Hemodynamic interactions of opioid-midazolam administration in the ICU have not been prospectively studied. However, hypotension and decreased stroke work indices were problematic during cardiac surgery when bolus dose midazolam was administered concurrently with fentanyl (90). Nonetheless, with titrated doses of midazolam and opioid, midazolam has been found to be a safe and effective adjuvant for cardiac surgery anesthesia, as the combination provides for lower catecholamine release when compared with separate drug therapy (91).

The issues of synergistic, additive, or antagonistic interactions between benzodiazepines and opioids are complex and may be species, site, drug, and effect dependent (92). For instance, one study (93) suggested that diazepam antagonized opioid-induced respiratory depression. In a retrospective study (94) of 43 ICU patients who received sufentanil infusions, those patients who also received midazolam infusions (0.07 mg/kg/hr) for >3 days had a higher incidence of increasing sufentanil requirements, hence indicating accelerated opioid tolerance in patients who received both infusions. In general, however, one should anticipate reduced requirements and more profound cardiorespiratory effects when midazolam and opioids are coadministered (2).

COMPARISON WITH OTHER SEDATIVE REGIMENS

Comparison with Lorazepam

Of all the benzodiazepines available in this country, midazolam and lorazepam are the two most commonly used for sedation in the ICU (95). Lorazepam, a benzodiazepine without active metabolites, has a longer time until the onset of the effect (lower lipid solubility) and a longer duration of the effect when compared with midazolam (1, 96). In addition, metabolism of lorazepam is less affected by advanced age or liver dysfunction (1). Lorazepam administration is associated with a stable hemodynamic profile, even when administered in conjunction with opioids (97). Lorazepam has been administered by intermittent injection or continuous infusion to patients in adult and pediatric ICUs (76). Toxic exposure to the drug vehicle, polyethylene glycol, was reported as the cause of acute tubular necrosis in a patient who received prolonged (43-day), high-dose lorazepam (98).

Oral lorazepam has been advocated to treat or prevent withdrawal from prolonged midazolam infusions in pediatric ICU patients and to allow for an earlier discharge home (76). Other studies (99, 100) have compared intravenous midazolam and lorazepam in controlled studies. Both lorazepam by intermittent bolus injections and midazolam by continuous infusion were found to be safe and effective for sedation in the ICU; no differences between hemodynamic or oxygen transport variables were noted. However, onset of sedation was slower with lorazepam (99). In a comparison study (100) with lorazepam infusions, the mean time to return to baseline mental status after midazolam infusions was 76 hrs, whereas the mean recovery time after lorazepam infusions was 11 hrs, although this difference was not statistically significant. Cost comparison data are most favorable for lorazepam.

Comparison with Propofol Infusions

Multiple studies have compared midazolam with propofol infusions for sedation in the ICU. In general, both have been found to be safe and effective in the early postoperative period. Propofol, especially with the loading dose, has an increased incidence of hypotension compared with midazolam (41, 101). For example, a 17% decline in blood pressure was observed with propofol administration in contrast to a 21% increase with midazolam during the initial hour of drug infusion, although neither change was clinically significant (102). During the induction of sedation, a 12% decrease in systolic blood pressure was reported in the midazolam group and a decrease of 24% in the propofol group ($p < .01$ [39]). Kox and Brydon (103) and Pappagallo et al. (45) observed significant decreases in mean arterial pressures (17 to 33 mm Hg) in the propofol groups with no significant change in hemodynamics for the midazolam groups.

Propofol was also associated with a decreased incidence of tachycardia (58% vs. 70%) and hypertension (39% vs. 54%) when compared with midazolam after coronary revascularization. There were no differences in myocardial ischemic events, however, between the groups (104). Roekaerts et al. (43) noted stable heart rates with propofol but relative tachycardia with midazolam infusions in similar postoperative patients; neither group had any incidence of myocardial ischemia. Vasodilator and opioid requirements were lower for postcardiac surgery patients who received propofol compared with those patients who received midazolam (41). Aitkenhead et al. (105) reported that heart rate was significantly lower among patients treated with propofol compared with those patients treated with midazolam, but there were no differences in blood pressure recordings between the groups.

Patients sedated with propofol infusions recover more rapidly, with less variability in recovery times, compared with patients sedated with midazolam infusions (3, 10, 38, 102, 105–107). Furthermore, alterations in the level of sedation are controlled more easily with propofol than with midazolam infusions (108, 109). Other studies have found no difference in the quality of sedation and no significant differences in the recovery times between propofol and midazolam groups (42, 101).

Hence, clinical studies demonstrate an increased incidence of hypotension with propofol administration, but a more rapid recovery of function after cessation of a propofol vs. midazolam infusion. The more rapid recovery with propofol can allow for lower costs overall. Prolonged infusions of propofol have been associated with hyperlipidemia due to the drug vehicle (107) In an *in vitro* study (110), propofol and thiopentone were associated with immune suppression, but midazolam produced no effect on immune function at clinically relevant doses. These findings are of potential importance in the critically ill patient.

Cost Comparison Analysis

Although cost is not necessarily a complication of drug administration, it is a factor when weighing the pros and cons of drug selection. There is over a ten-fold range in the cost of sedative drugs (95). Pharmacoeconomic analysis includes not only the cost of drug but also the total cost of care and effectiveness of therapy (96). For example, decreased recovery times with propofol led to reduced cost of sedation for short-term (<24 hrs) intensive care, despite an increased cost of propofol *per se* (17). A cost/benefit analysis comparing infusions of varying duration noted that propofol generates greater savings than midazolam only if the infusions were <24 hrs, although the savings were marginal (equivalent of $18) (111). However, in a more recent study (112), the cost of care was lower in the propofol vs. midazolam group by over $1,300 due to the difference in weaning times, even with longer infusions (average 5.8 days).

Based on pharmacoeconomic analysis, lorazepam is the drug of choice for long-term sedation in the ICU; practice parameters published by the American College of Critical Care Medicine and the Society of Critical Care Medicine recommended the use of lorazepam for sedation of >24 hrs duration (8, 99). Lorazepam also offers economic advantages for patients who are difficult to sedate and who require high-dose therapy (96, 113).

The sedative properties of midazolam can offer distinct advantages to help patients tolerate mechanical ventilation in the intensive care unit.

CONCLUSIONS

The sedative properties of midazolam can offer distinct advantages to help patients tolerate mechanical ventilation in the ICU. Midazolam has a rapid onset and short duration of sedative action which allow the drug to be administered by continuous infusion at variable infusion rates, according to the desired clinical level of sedation. Minimal adverse hemodynamic and respiratory effects are associated with the use of midazolam for the critically ill patient who receives mechanical ventilatory support. To avoid hypotension, hypovolemia should be corrected before midazolam administration. The dose of midazolam should be determined on an individual basis and titrated to the desired state of sedation as appropriate for clinical needs, patient physical status, age, and concurrent diseases and medications. Monitoring for the development of tolerance, withdrawal, or undesirable neurobehavioral effects should be an ongoing process. To minimize the incidence of withdrawal phenomena after long-term duration infusions, tapering, rather than abrupt termination, should be planned. Titration of midazolam infusion rates should also help to minimize prolonged sedative effects. However, due to altered kinetics in some critically ill patients, delayed emergence can occur. Propofol is associated with a lower incidence of delayed weaning from mechanical ventilation. Lorazepam has been recommended as the cost-effective drug of choice for prolonged sedation. Finally, continuous infusion of midazolam provides effective sedation for tolerance of mechanical ventilation. Overall, there have been few complications with its use in the critically ill population.

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LABELING CHANGES FOR PROPOFOL

From time to time, the Food and Drug Administration issues labeling changes for drugs administered to critically ill patients. The following paragraph was recently added to the precautions section for Diprivan (propofol, Zeneca Pharmaceuticals):

> "Very rarely, cases of unexplained postoperative pancreatitis (requiring hospital admission) have been reported after anesthesia in which DIPRIVAN Injectable Emulsion was one of the induction agents used. Due to a variety of confounding factors in these cases, including concomitant medications, a causal relationship to DIPRIVAN Injectable Emulsion is unclear."